

REMARKS

Claims 401, 411, 412, 414, 416-419, 422-424, 437-438, 462 and 464-467 are pending. Claims 463 and 468 are cancelled without prejudice as drawn to non-elected inventions. Applicants reserve the right to pursue the subject matter of these claims in one or more continuing applications. Claims 401, 411, 412, 414, 422 and 462 are amended. No new matter is added.

35 U.S.C. § 103(a) Rejections

Claims 401, 411, 412, 414, 416-419, 422-424, 437-438, 462 and 464-467 are rejected under 35 U.S.C. § 103(a) as being unpatentable over US Patent Publication No. 2002/0159984) to Brown ("Brown"). Specifically, the Examiner asserts that rather than being essential to the invention as claimed, nicotinamide is merely "...one of the medium components". On the basis of this (incorrect) assertion, the Examiner alleges that it would have been obvious for one of skill in the art to "optimize the ranges of concentration" of nicotinamide in the IMDM as taught by Brown, to arrive at the methods of the claimed invention. *See*, Office Action at pages 4-6.

Applicants traverse the rejection with respect to the pending claims as amended herein.

Claims 401, 411, 412 and 462 (from which the remaining claims subject to the rejection depend are amended to recite "...as compared to CD34+ cells cultured in the presence of nutrients and cytokines without exogenously added nicotinamide, nicotinamide analog or nicotinamide derivative...", thereby further affirming the essentiality of the presence of exogenously added nicotinamide, nicotinamide analog or nicotinamide derivative to the claimed invention. These essential features, as described in further detail *infra*, are not taught or suggested by Brown.

Moreover, regarding the essentiality of nicotinamide to the invention as claimed, Applicant wishes to point out that the disclosure teaches, in an unequivocal manner, that *ex-vivo* expansion and inhibition of differentiation of hematopoietic stem and progenitor cells, according to the claimed invention, requires providing nicotinamide. For example, in Example 5, Figures 14-18 and Table 5, expansion of hematopoietic stem cells with nicotine is compared to "controls", which include an identical medium without nicotinamide:

Hematopoietic CD34+ cell cultures were initiated in the presence of a combination of 5 cytokines, SCF, TPO, FLt3, IL-6 and IL-3, with or without different concentrations of nicotinamide. Following three weeks incubation period, the CD34+ cells were re-selected from culture by

affinity re-purification method and were enumerated. The results, presented in Figure 14, show that cultures supplemented with 1 and 5 mM nicotinamide yielded 99×10^4 and 180×10^4 CD34+ cells per ml, respectively, as compared with only 35×10^4 CD34+ cells per ml in the non-treated (cytokines only) control.

Thus, it is clear that it is the presence of nicotinamide, and not other components of the medium, which is responsible for the observed increased expansion of hematopoietic stem cells. Thus, Applicant submits that, contrary to the Examiner's assertion in the instant communication, exogenously added nicotinamide, as evidenced by the instant specification, is ***the essential component*** for achieving the hematopoietic stem cell expansion of the invention as claimed (**emphasis added**).

Further, the Examiner asserts that Brown recognizes that the "concentration of essential components of the IMDM including nicotinamide for expansion of CD34+/CD38- cells *ex-vivo* is a result effective variable depending on the desired use...". Applicant strongly disagrees.

Brown merely lists nicotinamide, along with 44 other compounds, as a component of IMDM. See, for example, Table I of Brown at page 4, left column. Further, Brown mentions that nicotinamide is one of a number of "...various vitamins and co-factors, such as riboflavin, nicotinamide, folic acid, choline, biotin, and the like that **may be required to sustain cell growth**" (**emphasis added**). See, for example, Brown at page 3, right hand column. Brown is silent with respect to the criticality of nicotinamide. In fact, nowhere in Brown is there any mention, suggestion or implication that the presence or concentration of nicotinamide is in any way associated with, critical to or important to the inhibition of stem cell differentiation or stem cell expansion, as required by the instant invention. Thus, not only does Brown not consider nicotinamide essential to the claimed culture medium and conditions, or worthy of "optimization", but one of ordinary skill in the art reading Brown would be unable to readily recognize the importance of nicotinamide for *ex-vivo* expansion and inhibition of differentiation of hematopoietic stem cells.

As such, Applicants respectfully request reconsideration and withdrawal of the present rejection.

35 U.S.C. § 102(b) Rejections

Claim 412 is rejected under 35 U.S.C. § 102(b) as being anticipated by US Patent No. 5,945,337 to Brown (“’337 patent”). Applicants traverse the rejection with respect to claim 412 as amended herein.

Claim 412 is amended to recite "...in the presence of exogenously added nicotinamide, nicotinamide analog or nicotinamide derivative for a culture period resulting in expanding a population of CD34+ hematopoietic stem cells while inhibiting differentiation of said CD34+ stem cells in said sample..." These features are not taught or suggested by the ’337 patent.

Rather, the ’337 patent teaches that the disclosed serum-free medium and disclosed methods support the “proliferation **and differentiation** of CD34+ cells” (**emphasis added**). See, for example, the 337 patent at column 1, lines 55-57, column 6, lines 8-11 and the Abstract. Thus, the ’337 patent does not teach all the limitations of claim 412 as amended. Applicants respectfully request reconsideration and withdrawal of the present rejection.

35 U.S.C. § 112, Second Paragraph, Rejections

The Examiner has rejected claims 414 and 422 under 35 U.S.C. § 112, 2nd paragraph, as being indefinite for failing to point out what is included or excluded by the claim language. The Examiner's rejections are traversed with respect to the claims as amended herein.

Claim 414 is amended to recite “said population of stem cells” which is recited in claim 401 from which 414 properly depends. Claim 422 is amended to recite “said combination of cytokines” which is recited in claim 401 from which 422 properly depends.

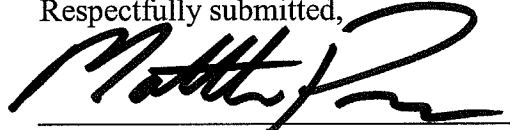
Therefore these rejections are moot and should be withdrawn.

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SERIAL NUMBER: 10/774,843

CONCLUSION

On the basis of the foregoing amendments, Applicants respectfully submit that the pending claims are in condition for allowance. Should any questions or issues arise concerning this application, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,



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